



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US91/02984</p> <p>(22) International Filing Date: 1 May 1991 (01.05.91)</p> <p>(30) Priority data: 518,364 3 May 1990 (03.05.90) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): G.D. SEARLE & CO. [US/US]; P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>) : CHEMBURKAR, Pramod, B. [US/US]; 48 Long Ridge Road, Randolph, NJ 07869 (US). FARHADIEH, Bahram [US/US]; 965 Sunrise Road, Libertyville, IL 60048 (US). STRUTHERS, Barbara, J. [US/US]; 1706 Garand Drive, Deerfield, IL 60015 (US). SCHUMANN, Steven, C. [US/US]; 10 N 819 S. Airlite St., Elgin, IL 60123 (US). KARARLI, Tugrul, T. [US/US]; 8335 N. Kildare, Skokie, IL 60076 (US).</p>		<p>(74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING IBUPROFEN AND A PROSTAGLANDIN</p> <p>(57) Abstract</p> <p>A pharmaceutical composition includes a core of an NSAID selected from ibuprofen and ibuprofen salts, which core is surrounded by an intermediate coating impermeable to the passage of ibuprofen and a mantle coating of a prostaglandin surrounding the coated ibuprofen core.</p>			

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PHARMACEUTICAL COMPOSITION CONTAINING
IBUPROFEN AND A PROSTAGLANDIN

Background of the Invention

The invention herein is directed to a new pharmaceutical composition which consists of a generally trilayer tablet having an inner core, an intermediate barrier coating and an outer mantle coating surrounding the inner core. The inner core includes the NSAID ibuprofen or a salt of ibuprofen. The mantle coating includes a prostaglandin, described hereinafter in more detail.

Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have long been recognized as having high therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis (OA) and rheumatoid arthritis (RA). While the NSAIDs present a beneficial therapeutic value they also exhibit undesirable side effects. An especially undesirable side effect of the administration of NSAIDs is the ulcerogenic effects generally associated with chronic use. The chronic use of NSAIDs, the use of high dosages of NSAIDs and the use of NSAIDs by the elderly can lead to NSAID induced ulcers. NSAID induced

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ulcers in the stomach can be dangerous. Such ulcers generally exhibit little or few symptoms and may cause dangerous bleeding when undetected. In some instances, bleeding ulcers can prove fatal. The United States Food and Drug Administration requires a class warning for all NSAIDs, which states: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.

Certain prostaglandins have been shown to prevent NSAID induced ulcers. Acceptable prostaglandin compounds for the invention herein and their preparation are described in U.S. Patents 3,965,143, 4,060,691, 4,271,314, and 4,683,328. The prostaglandin compound commercially available under the USAN (United States Adopted Name) name misoprostol is a pharmaceutically acceptable prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States. Misoprostol is commercially available by prescription in such countries.

While prostaglandins are beneficial compounds and have found therapeutic usage, prostaglandins are generally considered highly unstable. Therefore, it is desirable to find prostaglandins with the desired anti-ulcerogenic

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properties and which can be stabilized or provided in stabilized formulations especially with respect to contemplated oral methods of delivery.

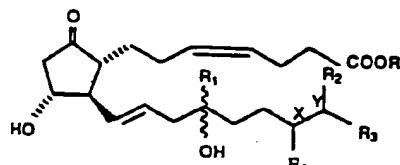
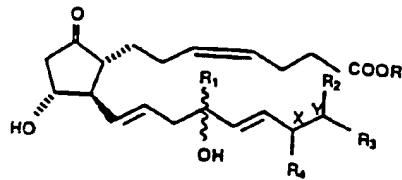
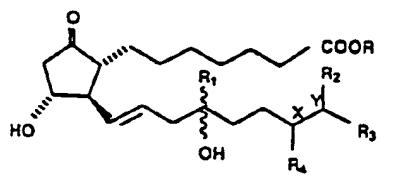
It would be desirable to provide a pharmaceutical composition which would exhibit the beneficial properties of an NSAID and which composition would exhibit the beneficial properties of a prostaglandin for countering (by inhibiting, reducing or preventing) the ulcerogenic side effects attendant to NSAID administration.

Summary of the Invention

The invention herein is directed to a pharmaceutical composition comprising a core consisting of an NSAID selected from ibuprofen and ibuprofen salts. An intermediate barrier coating surrounds the core. Such an intermediate coating prevents contact between the NSAID and the prostaglandin to thereby inhibit any deleterious or otherwise non-beneficial interaction of the NSAID and prostaglandin such as degradation of the prostaglandin by the NSAID. A mantle coating of a prostaglandin surrounds the core and intermediate coating. The prostaglandin preferably is an orally available prostaglandin.

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Acceptable prostaglandins for use herein include prostaglandins having the following structure



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R₁ represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R₂, R₃, and R₄ are hydrogen or lower alkyl having 1 to 4 carbon atoms or R₂ and R₃ together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R₃ or R₄ together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

An especially preferred pharmaceutical composition herein has a structure wherein the core comprises the NSAID ibuprofen in a therapeutic amount such as from 300 to 800 milligrams (mg), an intermediate coating comprising

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a material impervious/impermeable to the ibuprofen, and a mantle coating surrounding the core consisting of misoprostol in a therapeutic amount of 100 to 200 micrograms (mcg). An especially preferred intermediate coating can be formed from a crystalline-forming material such as a sugar, and more specifically sucrose.

The invention herein will be more fully understood with regard to the following brief description of the accompanying drawings and the following detailed description.

Brief Description of the Drawings

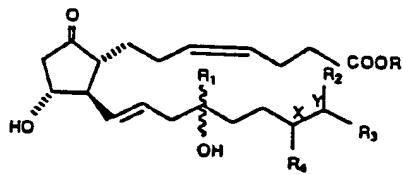
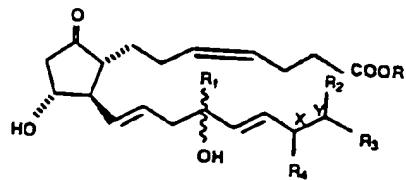
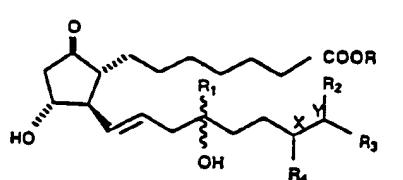
Figure 1 is a schematic representation of a tablet comprising the pharmaceutical composition herein.

Detailed Description of the Invention

The invention herein is directed to a pharmaceutical composition which is a generally trilayer tablet consisting of a core of the nonsteroidal anti-inflammatory drug (NSAID), ibuprofen and ibuprofen salts. Ibuprofen is the USAN name for (+)-2-(*p*-isobutylphenyl)-propionic acid. Surrounding the core is an intermediate

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coating of an impervious/impermeable material to the ibuprofen. An especially preferred intermediate coating can be formed from a crystalline forming material such as a sugar, and more specifically sucrose. Surrounding the core and intermediate coating is a mantle coating which consists of a prostaglandin of the structure



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R₁ represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R₂, R₃, and R₄ are hydrogen or lower alkyl having 1 to 4 carbon atoms or R₂ and R₃ together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R₃ or R₄ together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

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The pharmaceutical composition herein can be described with regard to the accompanying drawings wherein Figure 1 schematically represents the preferred embodiment of the composition herein.

Figure 1 represents a cross sectional view of a pharmaceutical composition herein. The pharmaceutical composition consists of a generally trilayer tablet 10 which can have any geometric shape but, as is shown in Figure 1, is preferably a bi-convex tablet. It should be noted that a bi-convex tablet can have a cylindrical shape between the convex surfaces, although for ease of description herein an oval cross section is shown. The tablet 10 includes an inner core 12 which includes the NSAID consisting of ibuprofen or its salt. The inner core 12 can be formulated by compressing the ibuprofen or ibuprofen salts in any suitable tableting equipment. Standard compression tableting techniques can be employed for forming the core.

The ibuprofen can be present in any therapeutically acceptable amount. For normal dosing of ibuprofen, ibuprofen is administered in a dosing range from 400 mg to 3200 mg per day. The Physicians' Desk Reference, 44th Edition, states that the recommended dosage for osteoarthritis and rheumatoid arthritis is 1200 to 3200 mg

per day in divided doses. For mild to moderate pain the recommended dosage is 400 mg every 4 to 6 hours as necessary for relief of pain. For dysmenorrhea the recommended dosage is 400 mg every 4 hours as necessary for the relief of pain. The inner core for the pharmaceutical composition herein therefore can be in an amount to accomplish such a dosing regimen and can contain from 150 to 800 mg of ibuprofen and preferably in a dosage of 400 mg. Various excipients can also be combined with the ibuprofen as is well known in the pharmaceutical art and including the inactive ingredients listed in the PDR 44th edition for ibuprofen as sold under the brand name and trademark MOTRIN by The Upjohn Company.

If the inner core is an ibuprofen salt, the ibuprofen salt can be present in a therapeutically acceptable amount as is referred to in the above discussion with respect to the acid.

Surrounding the core 12 is a barrier or an intermediate coating 14. The intermediate coating 14 can be any suitable coating which prevents passage of the ibuprofen. Ibuprofen is a compound that exhibits sublimation. Therefore an intermediate coating material is selected from those materials which prevent the passage of such a gaseous phase. It has been found herein that

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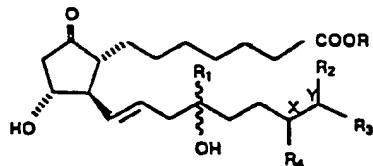
crystalline forming materials are impervious to ibuprofen in a gas phase. Any material which forms a crystalline structure can be used for the intermediate coating. An especially preferred class of compounds which can be used include crystalline forming sugars and more preferably sucrose. Sucrose is especially preferred as it exhibits crystalline properties at 55°C and it remains in the crystalline state and does not absorb any appreciable amounts of water up to a very high relative humidity value (84%). The intermediate coating 14 segregates the NSAID from the prostaglandin. The intermediate coating 14 prevents the degradation of the prostaglandin by the presence of the NSAID. Studies have shown that an admixture of misoprostol and ibuprofen is undesirably unstable for a commercially acceptable product. Solid state stability studies have shown that misoprostol is extremely unstable in the presence of ibuprofen and degrades at a rapid rate. A 10:1 mixture of ibuprofen:misoprostol stored at 55°C yields only 44% misoprostol after 4 days and only 18% after storage at 65°C for 3 days. It is, therefore, highly desirable to formulate a composition (dosage form) which would effectively separate the two active ingredients while providing a delivery system for each ingredient.

Additional studies have shown that an intermediate coating of certain polymers is unacceptable due to ibuprofen bleed through of the polymer which ibuprofen then interacts with and degrades the misoprostol. The intermediate coating can be coated onto the inner core using standard coating techniques. For example, aqueous or solvent coating techniques can be used to apply the coating to the inner core.

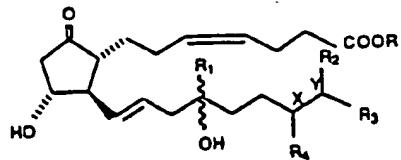
The mantle coating 16 surrounds the inner core of the NSAID and the intermediate coating, encapsulating the intermediate coated NSAID core. The mantle coating includes of a prostaglandin and more preferably an orally available prostaglandin. The mantle coating can be applied by compression coating or solvent coating techniques such as are well known in the tabletting art.

The terms "prostaglandin" and/or its accepted acronym "PG" or, as more appropriately for the E-series prostaglandins, "PGE," are used herein to refer to naturally occurring or man-made E-series prostaglandins and their analogs and derivatives.

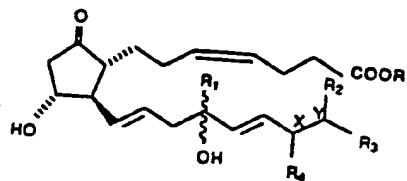
It has been found herein that acceptable prostaglandins include the E₁ prostaglandins shown by the following Formula I



E_2 prostaglandins shown by the following Formula II



and E_3 prostaglandins shown by the following Formula III

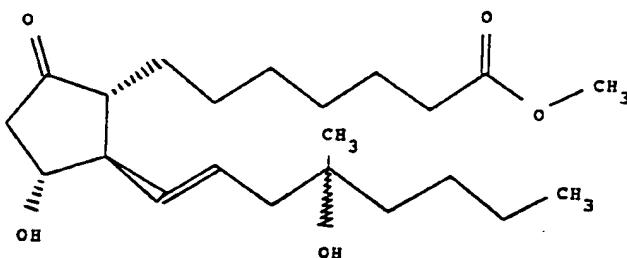


wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R_1 represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R_2 , R_3 , and R_4 are hydrogen or lower alkyl having 1 to 4 carbon atoms or R_2 and R_3 together with carbon Y form a cycloalkenyl having 4 to 6 carbon atoms or R_3 or R_4 together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

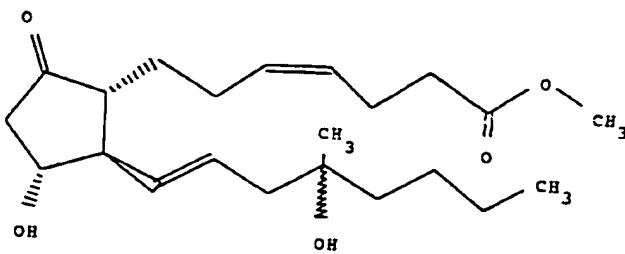
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By lower alkyl is meant straight or branched chain alkyl such as methyl, ethyl, propyl, isopropyl, butyl, secondary butyl or tertiary butyl, pentyl, or hexyl with the indicated limitation of the number of carbon atoms. With regard to the illustrated structures, the dashed line indicates the grouping being behind the plane of the paper and the solid, blackened triangular shape indicates that the group is in front of the plane of the paper.

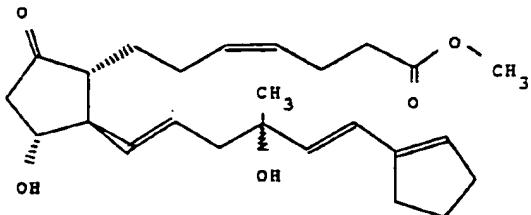
It has been found herein that acceptable prostaglandins include the prostaglandin misoprostol represented by the following Formula:



the prostaglandin enisoprost, (+)-methyl 11α,16-dihydroxy-16-methyl-9-oxoprosta-4Z,13E-dien-1-oate represented by the following Formula:



and the prostaglandin methyl 7-[2B-[6-(1-cyclopenten-1-yl)-4-hydroxy-4-methyl-1E,5E-hexadienyl]-3 α -hydroxy-5-oxo-1R,1 α -cyclopentyl]-4Z-heptenoate represented by the following formula:



With regard to the illustrated structures, the dashed line indicates the grouping being behind the plane of the paper and the solid, blackened triangular shape indicates that the group is in front of the plane of the paper.

The prostaglandins useful in the composition herein can be prepared by known reaction schemes such as by the methods taught in U.S. Patents 3,965,143, 4,271,314 and 4,683,328. The individual isomers can be obtained by chromatographic separation.

When the prostaglandin is misoprostol, (\pm)methyl 11 α ,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate, the misoprostol can be present in an amount from 50 to about 500 mcg and preferably from 100 to about 200 mcg.

The invention will be further understood with regard to the following examples.

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Example 1

A pharmaceutical composition was prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The tablet had the following composition.

Component	Unit Formula (mg)
- ibuprofen	400.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.10
hydroxypropyl methylcellulose	9.90
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

Example 2

A pharmaceutical composition was prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The composition had the following composition.

Component	Unit Formula (mg)
ibuprofen	600.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.20
hydroxy propyl methyl cellulose*	20.0
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

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Example 3

A pharmaceutical composition is prepared consisting of an ibuprofen central core, a sucrose intermediate coating and a misoprostol mantle. The composition has the following composition.

Component	Unit Formula (mg)
ibuprofen	800.00
pregelatinized cornstarch	155.00
croscarmallose sodium	43.00
stearic acid	12.30
acacia	5.00
sugar (sucrose)	29.00
misoprostol:HPMC dispersion (1:100)	
misoprostol	0.20
hydroxy propyl methyl cellulose*	20.0
colloidal silicon dioxide	4.60
calcium sulfate	77.00
starch U.S.P.	41.00
HPMC 6 cps (Pharmacoat 606)	58.50

Example 4

The following polymers were evaluated as barriers to ibuprofen sublimation. The determination of their abilities to perform as a barriers was made by bromocresol green (BCG) indicator or by misoprostol degradation. The BCG was applied in the outer coating rather than misoprostol. The BCG coating initially was a bright shade of blue when applied but as it came into contact with the acidic ibuprofen a color change occurred and shades of green to yellow were observed.

Hydroxypropyl methylcellulose 6 cps (aqueous)

Ethyl cellulose (aqueous)

Eudragit E30D (aqueous)

Eudragit E100 (ethanol)

Polyvinyl alcohol (ethanol)

Shellac (aqueous, ethanol)

Polyvinyl acetate phthalate (aqueous)

Cellulose acetate phthalate (methylene chloride-acetone)

The observed stability data showed rapid and extensive misoprostol degradation for all of the polymer barriers tested.

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Example 5

The following chemical barriers were evaluated to determine their efficacy as barriers to ibuprofen as the acid molecule.

Aluminum hydroxide/HPMC

Aluminum hydroxide/Eudragit E30D

Tricalcium Phosphate/HPMC

- Calcium oxide/HPMC

Magnesium hydroxide/HPMC

Magnesium oxide/HPMC

The observed stability data showed rapid and extensive misoprostol degradation for all of the chemical barriers tested.

The composition that is the invention herein provides an ease of delivery of the NSAID ibuprofen for its therapeutic value such as the alleviation of inflammation in a system which limits the undesirable side effects of such NSAID therapy. That is, the composition herein consisting of a generally trilayer tablet provides a prostaglandin in combination with the NSAID ibuprofen whereby the prostaglandin can be administered for its beneficial therapeutic value in preventing and/or inhibiting the incidence of NSAID induced ulcers.

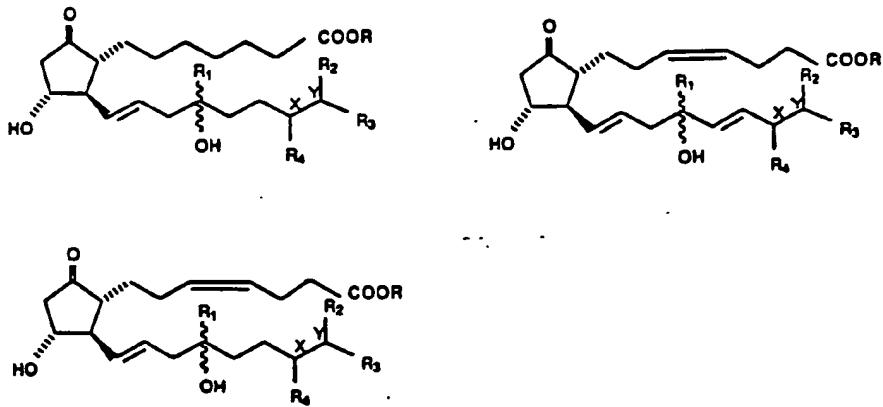
A particularly beneficial aspect of the invention herein is that the combination of the two components in a trilayer tablet assures compliance with the therapeutic regimen of the two active components. That is, a co-administration of the active components (ibuprofen and prostaglandin) separately can be difficult to achieve and can be difficult for a patient to faithfully follow. By placing the two active components in the same tablet or composition, adherence to the therapeutic regimen is controlled as the administration of the tablet containing the NSAID assures compliance of the administration of the prostaglandin.

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The composition herein is especially utile as the composition herein exhibits a stability for the prostaglandin and the ibuprofen in such a fixed combination as herein described.

Claims

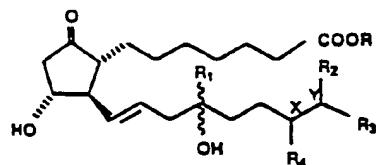
1. A pharmaceutical composition comprising:
 - a. a core consisting of an NSAID selected from ibuprofen and ibuprofen salts; and
 - b. an intermediate coating surrounding the core
 - c. a mantle coating surrounding the core consisting of a prostaglandin of the structural formula



wherein R represents hydrogen or lower alkyl having 1 to 6 carbon atoms, R₁ represents hydrogen, vinyl or lower alkyl having 1 to 4 carbon atoms and the wavy line represents R or S stereochemistry; R₂, R₃, and R₄ are hydrogen or lower alkyl having 1 to 4 carbon atoms or R₂ and R₃ together with carbon Y

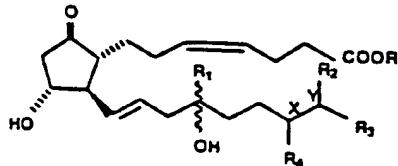
form a cycloalkenyl having 4 to 6 carbon atoms or R₃ or R₄ together with carbons X and Y form a cycloalkenyl having 4 to 6 carbon atoms and wherein the X-Y bond can be saturated or unsaturated.

2. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises a prostaglandin - of the structural formula



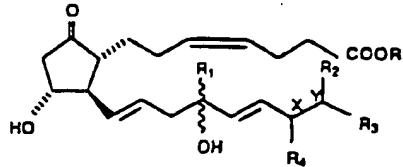
3. A pharmaceutical composition as recited in Claim 2 wherein the prostaglandin comprises misoprostol.

4. A pharmaceutical composition as recited in Claim 1 wherein the prostaglandin comprises the structural formula



5. A pharmaceutical composition as recited in Claim 4 wherein the prostaglandin comprises enisoprost.

6. A pharmaceutical composition as recited in Claim 1
wherein the prostaglandin comprises a structural
formula



7. A pharmaceutical composition as recited in Claim 1
wherein the NSAID comprises ibuprofen.
8. A pharmaceutical composition as recited in Claim 1
wherein the NSAID comprises an ibuprofen salt.
9. A pharmaceutical composition as recited in Claim 1
wherein the intermediate coating comprises a sucrose
coating.
10. A pharmaceutical composition as recited in Claim 1
wherein the prostaglandin mantle coating comprises a
stabilized prostaglandin formulation.
11. A pharmaceutical composition as recited in Claim 1
wherein the NSAID comprises ibuprofen from about 150
to 800 mg, the intermediate coating comprises sucrose
and the mantle coating comprises a stabilized

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prostaglandin formulation containing about 100 to 200
mcg of misoprostol.

12. A method of treating inflammation comprising
administering to a patient in need of such treatment,
a therapeutically effective amount of a composition
according to Claim 1.

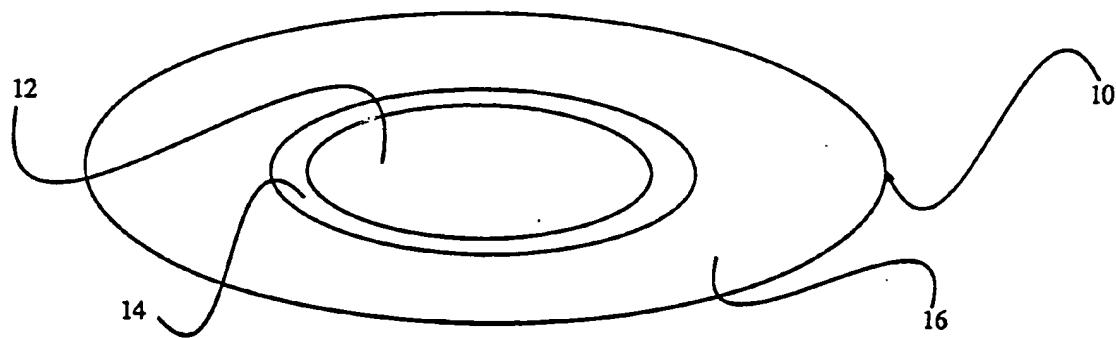


FIG 1

INTERNATIONAL SEARCH REPORT

International Appl. No. PCT/US 91/02984

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁹			
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 9/24 A 61 K 31/19 A 61 K 31/557			
II. FIELDS SEARCHED			
Minimum Documentation Searched ⁷			
Classification System	Classification Symbols		
Int.C1.5	A 61 K		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹			
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	
A	EP,A,0298666 (AMERICAN HOME PRODUCTS CORP.) 11 January 1989, see page 2, lines 1-2; pages 16-18, examples 11,12; claims 1,10 ---	1,7-9, 11	
A	DE,A,2363963 (ALZA CORP.) 11 July 1974, see page 2, paragraph 1; pages 35,36, examples 19,20,21 ---	1-6,10	
A	EP,A,0202112 (MAY & BAKER LTD) 20 November 1986, see page 1, line 13 - page 2, line 14; page 7, example 2 ---	1-6	
A	US,A,4301146 (D.R. SANVORDEKER) 17 November 1981, see column 1, lines 26-54; column 2, example 1 ---	1-6 -/-	
* Special categories of cited documents :¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
IV. CERTIFICATION			
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report		
03-09-1991	26.09.91		
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. PEIS <i>M. Peis</i>		

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A

GB,A,2135881 (FARMITALIA CARLO ERBA S.p.A.) 12 September 1984, see page 5, lines 46-57; page 11, formulation 1; claims

1

V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim numbers 12 because they relate to subject matter not required to be searched by this Authority, namely:

Pls. see Rule 39.1(iv) - PCT:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 64(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest
 No protest accompanied the payment of additional search fees

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9102984
SA 48471

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/09/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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